JAMA, The Journal of the American Medical Association
Issue: Volume 273(3), 18 Jan 1995, pp 199-208

Publication Type: [Original Contributions]
ISSN: 0098-7484
Accession: 00005407-199501180-00022

[Original Contributions]

Effects of Estrogen or Estrogen/Progestin Regimens on Heart Disease Risk Factors in Postmenopausal Women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial

The Writing Group for the PEPI trial.

Abstract

Objective: To assess pairwise differences between placebo, unopposed estrogen, and each of three estrogen/progestin regimens on selected heart disease risk factors in healthy postmenopausal women.

Design: A 3-year, multicenter, randomized, double-blind, placebo-controlled trial.

Participants: A total of 875 healthy postmenopausal women aged 45 to 64 years who had no known contraindication to hormone therapy.

Intervention: Participants were randomly assigned in equal numbers to the following groups: (1) placebo; (2) conjugated equine estrogen (CEE), 0.625 mg/d; (3) CEE, 0.625 mg/d plus cyclic medroxyprogesterone acetate (MPA), 10 mg/d for 12 d/mo; (4) CEE, 0.625 mg/d plus consecutive MPA, 2.5 mg/d; or (5) CEE, 0.625 mg/d plus cyclic micronized progesterone (MP), 200 mg/d for 12 d/mo.

Primary Endpoints.Four endpoints were chosen to represent four biological systems related to the risk of cardiovascular disease: (1) high-density lipoprotein cholesterol (HDL-C), (2) systolic blood pressure, (3) serum insulin, and (4) fibrinogen.

Analysis: Analyses presented are by intention to treat. P values for primary endpoints are adjusted for multiple comparisons; 95% confidence intervals around estimated effects were calculated without this adjustment.

Results: Mean changes in HDL-C segregated treatment regimens into three statistically distinct groups: (1) placebo (decrease of 0.03 mmol/L (1.2 mg/dL)); (2) MPA regimens (increases of 0.03 to 0.04 mmol/L (1.2 to 1.6 mg/dL)); and (3) CEE with cyclic MP (increase of 0.11 mmol/L (4.1 mg/dL)) and CEE alone (increase of 0.14 mmol/L (5.6 mg/dL)). Active treatments decreased mean low-density lipoprotein cholesterol (0.37 to 0.46 mmol/L (14.5 to 17.7 mg/dL)) and increased mean triglyceride (0.13 to 0.15 mmol/L (11.4 to 13.7 mg/dL)) compared with placebo. Placebo was associated with a significantly greater increase in mean fibrinogen than any active treatment (0.10 g/L compared with -0.02 to 0.06 g/L); differences among active treatments were not significant. Systolic blood pressure increased and postchallenge insulin levels decreased during the trial, but neither varied significantly by treatment assignment. Compared with other active treatments, unopposed estrogen was associated with a significantly increased risk of adenomatous or atypical hyperplasia (34% vs 1%) and of hysterectomy (6% vs 1%). No other adverse effect differed by treatment assignment or hysterectomy status.

Conclusions: Estrogen alone or in combination with a progestin improves lipoproteins and lowers fibrinogen levels without detectable effects on postchallenge insulin or blood pressure. Unopposed estrogen is the optimal regimen for elevation of HDL-C, but the high rate of endometrial hyperplasia restricts use to women without a uterus. In women with a uterus, CEE with cyclic MP has the most favorable effect on HDL-C and no excess risk of endometrial hyperplasia.

(JAMA. 1995;273:199-208)

Meta-analyses of observational studies suggest a 50% reduction in heart disease risk in postmenopausal women taking estrogen [1,2,3]. Most of these studies were conducted in the United States where a conjugated equine estrogen (CEE) preparation taken orally without a progestin (unopposed estrogen) has been the most commonly used regimen. Recent observational studies [4,5,6] suggest that estrogen/progestin regimens (recommended to prevent estrogen-induced endometrial cancer) have a cardioprotective effect similar to unopposed estrogen.

Several biologically plausible mechanisms have been proposed for estrogen-mediated cardioprotection [7,8,9,10], including estrogen-associated changes in lipid metabolism, blood pressure, carbohydrate metabolism, coagulation factors, and endothelial function. One of the most attractive mechanisms is the favorable effect of unopposed oral estrogens on lipoproteins, increasing high-density lipoprotein cholesterol (HDL-C) and decreasing low-density lipoprotein cholesterol (LDL-C) levels by 10% to 15% [11,12,13,14]. Prospective studies suggest that HDL-C is the best predictor of coronary heart disease risk in women [15,16,17], and that up to half of the apparent cardiovascular benefit observed in estrogen-treated women may be mediated by the higher HDL-C levels [18,19].

The addition of a progestin to estrogen therapy has been considered problematic because progestins have been hypothesized or shown to blunt, block, or even overwhelm estrogenic effects, particularly on lipoproteins [20,21]. Two large cross-sectional studies [22,23] found that women treated with estrogen plus progestin had equivalent or more favorable levels of heart disease risk factors than women treated with unopposed estrogen. However, a recent clinical trial [24] reported that women taking unopposed CEE had significantly greater increases of HDL-C than women taking CEE plus continuous medroxyprogesterone acetate (MPA). Thus, there is concern that many women are using estrogen/progestin regimens, some to prevent heart disease, with limited and contradictory information available about the metabolic effects of these drugs.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial was designed to determine the differences in selected heart disease risk factors (HDL-C, fibrinogen, insulin, and blood pressure) in postmenopausal women treated with placebo, unopposed estrogen, or one of three combined estrogen/progestin regimens.

METHODS

Design and Overview

Details of the rationale and study design are in press [25,26,27,28]. Briefly, PEPI was a randomized, double-blind, placebo-controlled trial carried out in seven clinical centers (see acknowledgment for PEPI sites) to compare the effect on selected heart disease risk factors of estrogen alone or in combination with one of three progestin regimens. The PEPI treatment regimens were those currently in use or expected to be used in the near future, at the time the study was designed in 1988. The decisions to use CEE as the trial estrogen and to include an unopposed estrogen treatment were made because nearly all of the observational data showing cardioprotection in estrogen users were based on the use of unopposed CEE. The decision to use MPA was based on clinical experience establishing endometrial protection with cyclic MPA and more limited data for continuous MPA regimens. Micronized progesterone (MP) was chosen because preliminary data suggested that this drug did not mask an estrogen-mediated increase in HDL-C [29,30]. Study medications and their matching placebos were provided by the following companies: CEE (Premarin, Wyeth-Ayerst Laboratories, Philadelphia, Pa); MPA (Provera, The Upjohn Company, Kalamazoo, Mich); and MP (Schering Plough, Kenilworth, NJ).

The primary endpoints were selected to represent four different biological/metabolic systems that were thought to be affected by estrogen use and to influence cardiovascular risk in women: lipid metabolism, blood pressure, carbohydrate metabolism, and coagulation/hemostasis. It was recognized at the outset that the size and duration of PEPI would not provide adequate power to determine whether any of these hormone regimens prevented cardiovascular disease.

An increased risk of endometrial hyperplasia was expected for unopposed estrogen (although the magnitude of the risk was unknown) and not expected for CEE and cyclic MPA; risks were uncertain for the other proposed regimens. Therefore, all women were required to undergo an endometrial aspiration biopsy at baseline and annually thereafter. Additional biopsy specimens were obtained if there was noncyclic endometrial bleeding. Because the relation of estrogen and estrogen/progestin combinations to breast cancer remains unknown, all women were also required to have baseline and annual mammograms.

Informed Consent

The institutional review board at each clinical center approved the PEPI protocol and consent forms. A description of the study risks and benefits was provided to all participants, who gave written informed consent for the screening visits (eligibility evaluation) at the initial screening visit and consent for the trial at the visit preceding randomization.

Participants

Women aged 45 to 64 years, with or without a uterus, were invited to participate in PEPI. Potential participants were recruited through mass media and community efforts, as detailed elsewhere [27]. Preliminary telephone screening was used to exclude clearly ineligible women (eg, age, serious illness, or unwilling to be in a clinical trial). Three screening clinic visits were scheduled to evaluate eligibility. Women were required to be naturally or surgically menopausal: if naturally menopausal, at least 1 year, but not greater than 10 years, past their last menstrual period; if surgically menopausal, at least 2 months after hysterectomy and with a follicle-stimulating hormone level greater than or equal to 40 IU/L. Normal baseline results of mammography and endometrial biopsy also were required.

Women who had severe menopausal symptoms were excluded (to minimize the potential for unblinding), as were women who had used estrogens or progestins within 3 months. Women treated with thyroid hormone who had not been taking a stable dose for at least 3 months and who did not have a normal thyroid-stimulating hormone level were also excluded. Other exclusion criteria were serious illness (eg, myocardial infarction within 6 months, congestive heart failure, stroke, transient ischemic attack) or contraindications to estrogen, including prior breast or endometrial cancer.

Laboratory exclusions included LDL-C level of 4.91 mmol/L or more (>=190 mg/dL) (n=90), triglyceride level of 12.93 mmol/L or more (>=500 mg/dL) (n=6), body mass index greater than or equal to 40 (n=17), blood pressure greater than or equal to 160 mm Hg systolic or 95 mm Hg diastolic (n=14); and fasting plasma glucose level of 7.7 mmol/L or more (>=140 mg/dL) (n=17).

Women who were eligible after the third screening visit were requested to take daily placebos resembling the study medications for 28 days in order to identify those unlikely to adhere to the PEPI protocol. Only eight women were excluded for compliance level less than 80%.

Randomization and Treatment

Between December 1989 and February 1991, the seven PEPI clinical centers randomized 875 women (60% of those attending the initial screening visit). Treatment assignment was determined by a computer program that verified all eligibility criteria prior to randomization. A blocked randomization scheme was used to assign eligible women in equal numbers to one of five treatment groups, stratified by clinical center and hysterectomy status. Because it was expected that women without a uterus would differ with regard to bleeding and subsequent unblinding, equal proportions of hysterectomized women were targeted to be randomized at each PEPI clinical center.

Women were randomized to one of the following treatments in 28-day cycles: (1) placebo; (2) CEE, 0.625 mg/d; (3) CEE, 0.625 mg/d, plus MPA, 10 mg/d for the first 12 days; (4) CEE, 0.625 mg/d, plus MPA, 2.5 mg/d; or (5) CEE, 0.625 mg/d, plus MP, 200 mg/d for the first 12 days.

All medications were taken orally. Pills and capsules were provided in blister packs designed to be opened once a day. Active drugs and placebo were prepared in identical forms. The 2.5- and 10-mg doses of MPA were specially prepared for identical appearance. All women took two pills (one of CEE or matching placebo and one of MPA or matching placebo) and two capsules (each with 100 mg of MP or matching placebo).

Follow-up and Measurements

Women were scheduled to be seen at 3, 6, and 12 months the first year after randomization and thereafter every 6 months for a total of 3 years. At every visit, a diary of symptoms, bleeding, medication use, and interim illness was reviewed. Unused pills were returned and counted to assess adherence. Blood pressure and weight were measured. Fasting morning blood was obtained for measurement of lipids and lipoproteins at 6 months and at each annual visit. Blood for insulin and glucose, before and after a glucose tolerance test, and for fibrinogen was obtained at years 1 and 3 of the trial. Physical examination, mammography, and endometrial biopsy were performed annually.

Demographic information, medical history, use of medications during the prior 2 weeks, physical activity, and lifetime use of cigarettes, alcohol, oral contraceptives, and noncontraceptive estrogens were ascertained using standardized questionnaires.

Height, weight, and waist and hip girth were measured with participants wearing light clothing and no shoes. Blood pressure was measured twice in resting, seated subjects according to a modification of the Hypertension Detection and Follow-up Protocol [31]. Venous blood was obtained in the morning after an overnight fast, and 2 hours later after a standard 75-g oral glucose tolerance test. Frozen plasma and serum samples were mailed overnight on dry ice to separate central laboratories for lipids, insulin and glucose, and fibrinogen determinations.

The Central Lipid Laboratory was one of the National Reference System for Cholesterol laboratories standardized according to Centers for Disease Control and Prevention methods. Cholesterol and triglyceride levels were determined on fasting EDTA plasma by enzymatic procedures [32]. High-density lipoprotein cholesterol was separated from plasma by precipitation of other lipoproteins, with dextran sulfate manganese and the supernate assayed enzymatically for cholesterol content [33]. Low-density lipoprotein cholesterol was determined directly by ultracentrifugation [34]. An assay was repeated if the coefficient of variation was greater than 1.5% for cholesterol or greater than 3% for triglyceride or HDL-C. Coefficients of variation demonstrated on control pools during PEPI analyses were cholesterol, 1.27%, triglyceride, 2.1%, and HDL-C, 2.62%.

Plasma glucose was measured by a colorimetric glucose oxidase method, following Somogyi precipitation [35]. The interassay coefficients of variation during PEPI analyses, based on Boehringer Mannheim Diagnostics control pools, were 2.0% and 1.8% for target glucose values of 3.94 and 16.09 mmol/L (71 and 290 mg/dL), respectively.

Serum insulin was assayed in duplicate using a minor modification of a double antibody method [36]. Based on Bio-Rad control pools, interassay coefficients of variation were 29%, 14%, and 13% for insulin target values of 49, 298, and 649 pmol/L, respectively. Because of an unexplained downward drift in the insulin levels during the course of the study, at the end of the trial, 100 masked samples obtained at 12 and 36 months were again assayed for 2-hour insulin; the correlation between these results and the original results was 0.92 for samples obtained at 12 months and 0.93 for samples obtained at 36 months.

Fibrinogen was assayed by the Dade method, based on the clotting time of fasting citrated plasma using excess thrombin [37]. During the period of analysis of PEPI samples and based on analysis of Dade control pools with target fibrinogen values of 2.38 to 2.62 g/L, the interassay coefficient of variation ranged from 1.2% to 3.8%.

Statistical Analysis

All hypothesis testing followed plans in the PEPI protocol and was by treatment assignment (intention to treat). General mixed linear models [38] were used to describe treatment differences for the primary and secondary outcome measures. These were fitted using restricted maximum likelihood and evaluated using F tests [39]; t tests were used to assess pairwise treatment differences. Treatment effects were assessed on either mean changes from baseline (eg, HDL-C, fibrinogen, and insulin) or rates of change based on linear models (blood pressure). All analyses included clinical center and hysterectomy status as covariates. According to protocol, when there was a baseline imbalance among the randomized treatment cohorts for an outcome measure, its baseline level was also included as a covariate. Three measures (triglyceride, insulin, and fibrinogen) exhibited right-skewed distributions; these data were log-transformed for analyses, and the estimates from analyses transformed back to the original scale for reporting.

PEPI was designed to provide statistical power exceeding 80% for detecting prespecified differences in each of the four primary outcome measures with the overall type 1 error controlled to be.05 [25]. The nominal P value from each of the four F tests was adjusted upward according to the Bonferroni method [40], using the approximation Bonferroni P=(1-(1-Nominal P)4). When Bonferroni P<.05, t tests were performed to assess differences between each of the ten possible pairs of the five treatments; P values from these t tests were adjusted in a parallel manner to control for the 40 (4x10) possible comparisons. In this article, the term "significant" is used to describe global or pairwise differences based on Bonferroni-adjusted P values for primary outcome measures and nominal P values for secondary outcome measures.

RESULTS

Women randomized to the five trial arms had similar sociodemographic, lifestyle, and menopause-related characteristics [26]. Overall, their average age was 56.1 years; 89% were white, 5% Hispanic, 4% African American, 2% Asian, and 0.5% Native American. Most were employed (67%) and married (65%). More than half had completed some college, had one to three children, and had previously used noncontraceptive estrogen. Forty-nine percent had never smoked, 50% drank more than 12 alcoholic beverages per year but less than 30 drinks per month, and almost two thirds reported at least moderate physical activity. Approximately 32% had a hysterectomy at an average age of 41.8 years.

Table 1compares the baseline values for the primary outcome variables and important secondary outcome measures among the five randomly assigned treatment groups. Two significant differences were found. Women assigned to placebo had higher mean levels of fibrinogen and LDL-C at baseline. As specified by the PEPI protocol, these baseline levels were included as covariates in subsequent analyses of treatment effects on fibrinogen and LDL-C.

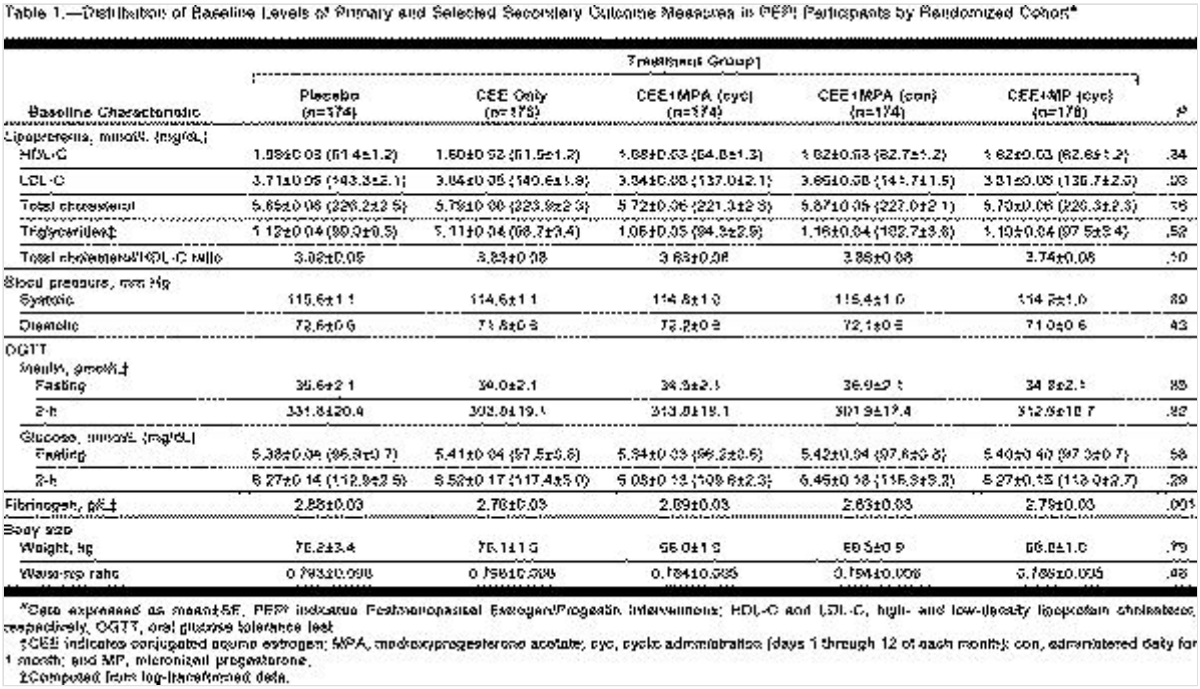

Table 1.—Distribution of Baseline Levels of Primary and Selected Secondary Outcome Measures in PEPI Participants by Randomized Cohort*

Baseline Characteristic	Treatment Group: Placebo (n=174)	CEE Only (n=175)	CEE+MPA (cyc) (n=174)	CEE+MPA (con) (n=174)	CEE+MP (cyc) (n=176)	P
Lipoproteins, mmol/L (mg/dL)						
HDL-C	1.58±0.03 (61.4±1.2)	1.60±0.02 (61.5±1.2)	1.68±0.03 (64.8±1.3)	1.62±0.03 (62.7±1.2)	1.62±0.03 (62.6±1.2)	.34
LDL-C	3.71±0.05 (143.3±2.1)	3.64±0.05 (140.6±1.9)	3.54±0.05 (137.0±2.1)	3.65±0.05 (141.7±1.9)	3.61±0.05 (139.7±2.0)	.03
Total cholesterol	5.65±0.06 (226.2±2.5)	5.78±0.06 (223.6±2.3)	5.72±0.06 (221.3±2.3)	5.87±0.06 (227.0±2.1)	5.70±0.06 (220.3±2.3)	.16
Triglycerides‡	1.12±0.04 (99.2±0.5)	1.11±0.04 (98.7±3.4)	1.05±0.05 (94.3±2.9)	1.16±0.04 (102.7±3.6)	1.10±0.04 (97.5±3.4)	.52
Total cholesterol/HDL-C ratio	3.62±0.05	3.83±0.05	3.63±0.05	3.86±0.05	3.74±0.05	.10
Blood pressure, mm Hg						
Systolic	115.6±1.1	114.6±1.1	114.8±1.0	115.4±1.0	114.7±1.0	.80
Diastolic	72.6±0.6	73.8±0.6	73.2±0.6	72.1±0.6	71.0±0.6	.43
OGTT						
Insulin, pmol/L‡						
Fasting	35.6±2.1	34.0±2.1	34.9±2.1	36.9±2.1	34.8±2.1	.85
2-h	331.8±20.9	302.0±19.1	313.0±19.1	301.9±17.4	312.9±18.7	.82
Glucose, mmol/L (mg/dL)						
Fasting	5.38±0.06 (96.9±1.7)	5.41±0.04 (97.5±0.8)	5.34±0.03 (96.2±0.6)	5.42±0.04 (97.6±0.8)	5.40±0.40 (97.3±0.7)	.58
2-h	6.27±0.14 (112.9±2.5)	6.52±0.17 (117.4±3.0)	6.08±0.13 (109.6±2.3)	6.45±0.16 (116.3±2.8)	6.27±0.15 (113.0±2.7)	.29
Fibrinogen, g/L‡	2.85±0.03	2.76±0.03	2.89±0.03	2.83±0.03	2.79±0.03	.001
Body size						
Weight, kg	76.2±3.4	76.1±1.6	66.0±1.6	69.5±0.9	66.8±1.6	.79
Waist-hip ratio	0.793±0.006	0.788±0.006	0.784±0.006	0.784±0.006	0.786±0.005	.48

*Data expressed as mean±SE. PEPI indicates Postmenopausal Estrogen/Progestin Interventions; HDL-C and LDL-C, high- and low-density lipoprotein cholesterol, respectively; OGTT, oral glucose tolerance test.
†CEE indicates conjugated equine estrogen; MPA, medroxyprogesterone acetate; cyc, cyclic administration (days 1 through 12 of each month); con, administered daily for 1 month; and MP, micronized progesterone.
‡Computed from log-transformed data.

Table 1. Distribution of Baseline Levels of Primary and Selected Secondary Outcome Measures in PEPI Participants by Randomized Cohort

Table 2shows the mean change (and 95% confidence interval) between baseline and follow-up measures for the primary outcome measures and related secondary outcomes. Also included are the results from analyses of covariance for differences among treatment arms. Nominal P values are provided to describe these differences; for the four primary outcome measures, Bonferroni-adjusted P values are also given. Of the four primary outcome measures, significant differences among the treatment arms were detected for HDL-C (Bonferroni P<.001) and fibrinogen (Bonferroni P<.001). Differences among arms for systolic blood pressure (Bonferroni P>.99) and 2-hour insulin (Bonferroni P=.74) were not statistically significant.

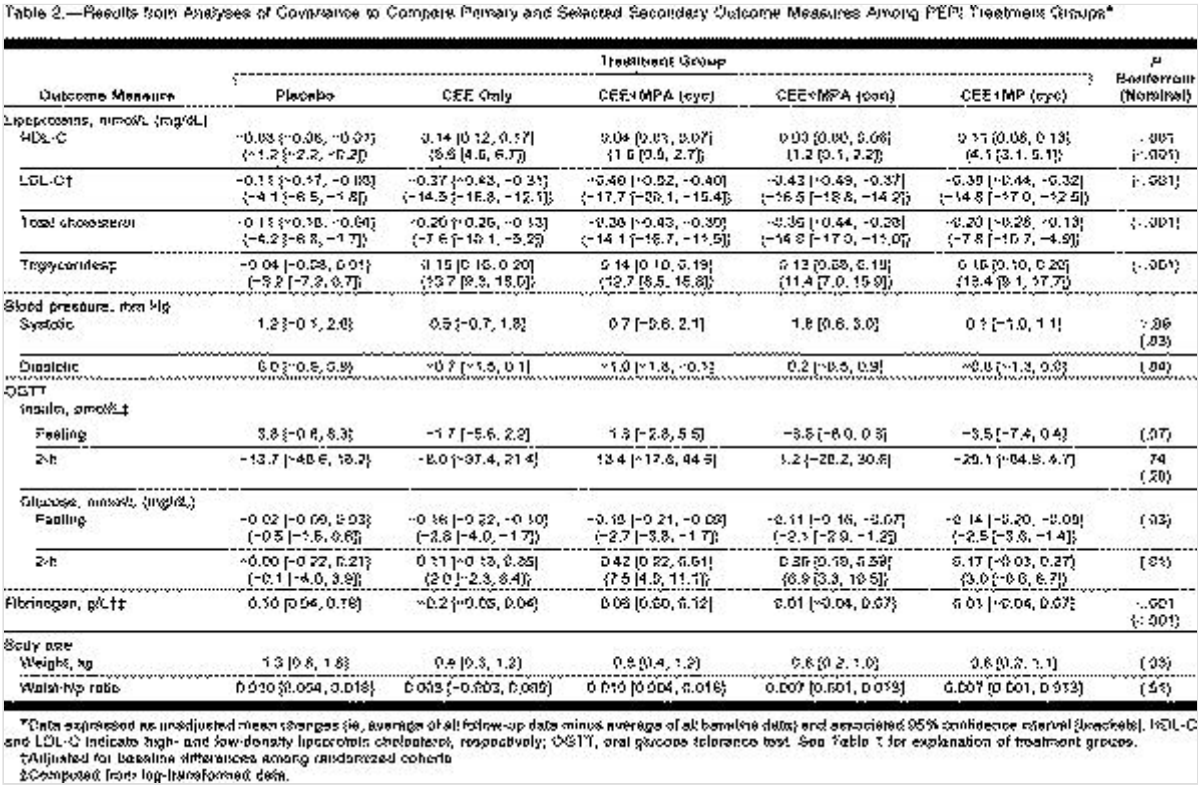

Table 2.—Results from Analyses of Covariance to Compare Primary and Selected Secondary Outcome Measures Among PEPI Treatment Groups*

Outcome Measure	Treatment Group: Placebo	CEE Only	CEE+MPA (cyc)	CEE+MPA (con)	CEE+MP (cyc)	P Bonferroni (Nominal)
Lipoproteins, mmol/L (mg/dL)						
HDL-C	−0.03 (−0.06, −0.01) (−1.2 [−2.2, −0.2])	0.14 (0.12, 0.17) (5.6 [4.6, 6.7])	0.04 (0.01, 0.07) (1.6 [0.5, 2.7])	0.03 (0.00, 0.06) (1.2 [0.1, 2.2])	0.17 (0.08, 0.13) (4.1 [3.1, 5.1])	<.001 (<.001)
LDL-C†	−0.13 (−0.17, −0.08) (−4.1 [−6.5, −1.6])	−0.37 (−0.43, −0.31) (−14.3 [−16.8, −12.1])	−0.48 (−0.52, −0.40) (−17.7 [−20.1, −15.4])	−0.43 (−0.49, −0.37) (−16.5 [−18.8, −14.2])	−0.39 (−0.44, −0.32) (−14.8 [−17.0, −12.5])	(<.001)
Total cholesterol	−0.13 (−0.18, −0.08) (−4.2 [−6.8, −1.7])	−0.26 (−0.29, −0.23) (−7.6 [−10.1, −5.2])	−0.36 (−0.43, −0.30) (−14.1 [−16.7, −11.5])	−0.35 (−0.44, −0.26) (−14.8 [−17.0, −11.0])	−0.20 (−0.26, −0.13) (−7.8 [−10.7, −4.9])	(<.001)
Triglycerides‡	−0.04 (−0.08, 0.01) (−3.2 [−7.2, 0.7])	0.15 (0.10, 0.20) (13.7 [9.3, 18.0])	0.14 (0.10, 0.19) (12.7 [8.5, 16.8])	0.12 (0.08, 0.16) (11.4 [7.0, 15.9])	0.15 (0.10, 0.20) (13.4 [9.1, 17.7])	(<.001)
Blood pressure, mm Hg						
Systolic	1.2 (−0.1, 2.6)	0.5 (−0.7, 1.8)	0.7 (−0.6, 2.1)	1.8 (0.6, 3.0)	0.1 (−1.0, 1.1)	>.99 (.03)
Diastolic	0.0 (−0.8, 0.9)	−0.7 (−1.5, 0.1)	−1.0 (−1.8, −0.3)	0.2 (−0.5, 0.9)	−0.8 (−1.3, 0.0)	(.04)
OGTT						
Insulin, pmol/L‡						
Fasting	3.8 (−0.6, 8.3)	−1.7 (−5.6, 2.2)	1.3 (−2.8, 5.5)	−3.5 (−8.0, 0.9)	−3.5 (−7.4, 0.4)	(.07)
2-h	−13.7 (−48.6, 18.2)	−8.0 (−37.4, 21.4)	13.4 (−17.8, 44.5)	1.2 (−28.2, 30.6)	−29.1 (−64.9, 4.7)	.74 (.20)
Glucose, mmol/L (mg/dL)						
Fasting	−0.02 (−0.09, 0.03) (−0.5 [−1.5, 0.6])	−0.16 (−0.22, −0.10) (−2.8 [−4.0, −1.7])	−0.18 (−0.21, −0.09) (−2.7 [−3.8, −1.7])	−0.11 (−0.16, −0.07) (−2.1 [−2.9, −1.2])	−0.14 (−0.20, −0.09) (−2.5 [−3.6, −1.4])	(.03)
2-h	−0.00 (−0.22, 0.21) (−0.1 [−4.0, 3.9])	0.31 (−0.13, 0.85) (2.0 [−2.3, 8.4])	0.42 (0.22, 0.61) (7.5 [4.0, 11.1])	0.35 (0.19, 0.50) (6.3 [3.3, 10.5])	0.17 (−0.03, 0.37) (3.0 [−0.6, 6.7])	(.01)
Fibrinogen, g/L‡	0.00 (0.04, 0.10)	−0.02 (−0.05, 0.04)	0.08 (0.00, 0.12)	0.01 (−0.04, 0.07)	0.03 (−0.04, 0.07)	<.001 (<.001)
Body size						
Weight, kg	1.3 (0.8, 1.8)	0.6 (0.3, 1.2)	0.8 (0.4, 1.2)	0.6 (0.2, 1.0)	0.8 (0.2, 1.1)	(.03)
Waist-hip ratio	0.010 (0.004, 0.016)	0.003 (−0.003, 0.009)	0.010 (0.004, 0.016)	0.007 (0.001, 0.013)	0.007 (0.001, 0.013)	(.01)

*Data expressed as unadjusted mean changes (ie, average of all follow-up data minus average of all baseline data) and associated 95% confidence interval (brackets). HDL-C and LDL-C indicate high- and low-density lipoprotein cholesterol, respectively; OGTT, oral glucose tolerance test. See Table 1 for explanation of treatment groups.
†Adjusted for baseline differences among randomized cohorts.
‡Computed from log-transformed data.

Table 2. Results from Analyses of Covariance to Compare Primary and Selected Secondary Outcome Measures Among PEPI Treatment Groups

Lipids and Lipoproteins

Each active treatment regimen was associated with a significantly greater increment in mean HDL-C levels than placebo (Bonferroni P<.001). The average increases in HDL-C levels were similar in women assigned to CEE alone (0.14 mmol/L (5.6 mg/dL)) or CEE with MP (0.11 mmol/L (4.1 mg/dL)), and these women had significantly greater HDL-C elevations (Bonferroni P<.004) than women assigned to CEE with cyclic or continuous MPA (0.04 and 0.03 mmol/L (1.6 and 1.2 mg/dL), respectively) Table 2. For all hormone regimens, HDL-C levels increased during the first 6 to 12 months and gradually decreased thereafter, although not to the baseline level Figure 1, top left).

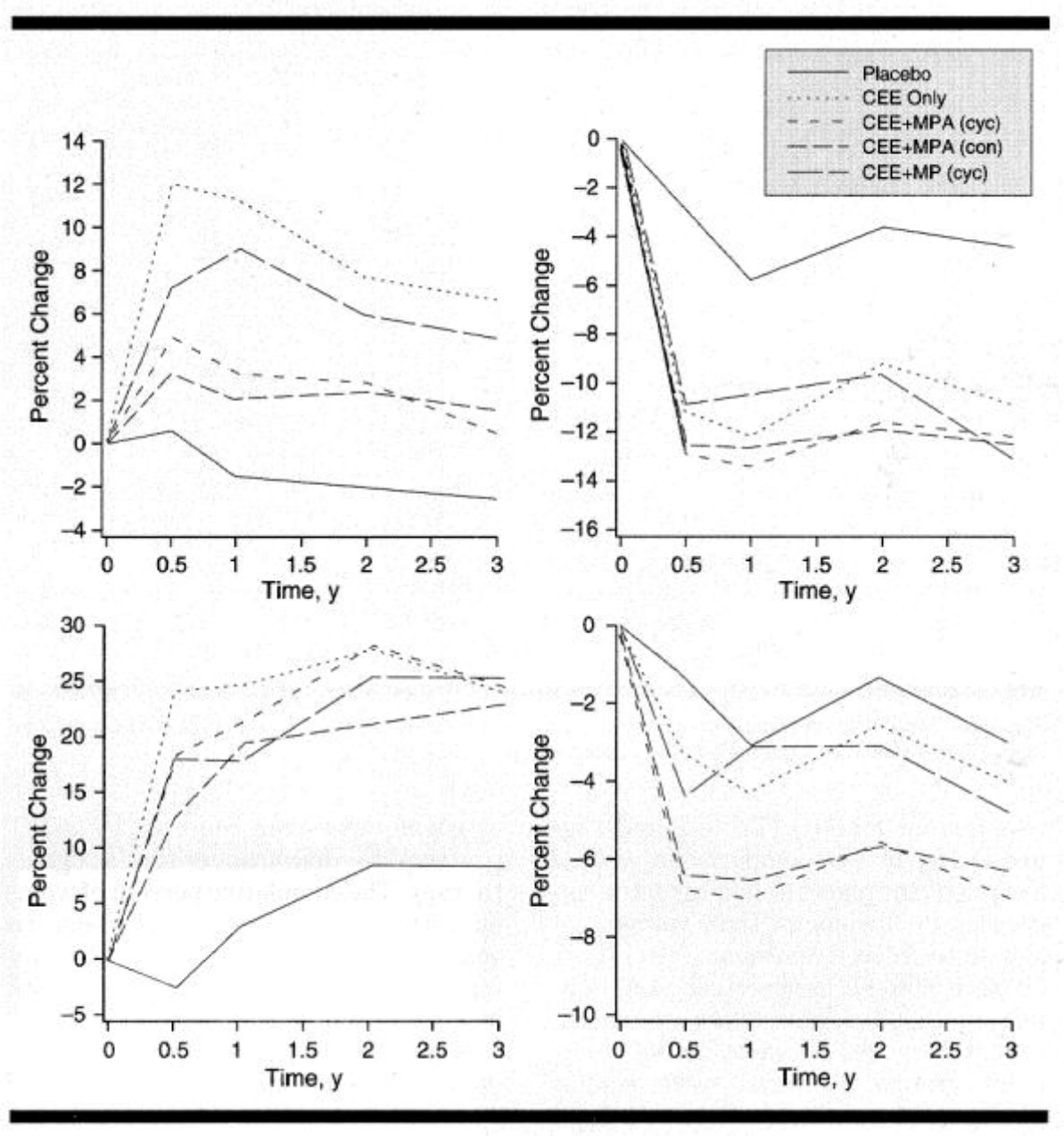

Figure 1. Mean percent change from baseline by treatment arm for high-density lipoprotien cholesterol (top left), left-density lipoprotein cholesterol (top right), triglycerides (botteom left), and total cholesterol (bottom right) See Table 1for explanation of treatment groups

Hysterectomized women taking unopposed estrogen (n=54) had HDL-C levels that were, on average, 0.14 mmol/L (5.5 mg/dL) greater at the end of the study than levels in women without a hysterectomy who were assigned to unopposed estrogen (n=114), consistent with the observation that many women with a uterus developed endometrial hyperplasia and were unable to continue unopposed estrogen. In a comparison limited to women who had a hysterectomy (women who were equally adherent to their medication), unopposed CEE was associated with significantly greater average increases in HDL-C than CEE plus MP, 0.19 mmol/L (7.53 mg/dL) vs 0.11 mmol/L (4.22 mg/dL) (P=.01).

Low-density lipoprotein cholesterol levels decreased to their lowest levels by 6 to 12 months and did not change significantly thereafter Table 2and Figure 1, top right). Changes were similar, averaging 0.41 mmol/L (15.9 mg/dL), and significantly different from placebo for all active treatment regimens (P<.001) and in women with or without a hysterectomy.

Triglyceride levels increased comparably in all active treatment arms from a mean of 2.54 mmol/L (98.3 mg/dL) to 2.87 mmol/L (111 mg/dL) and differed significantly from placebo (P<.001) Table 2and Figure 1, bottom left). Compared with placebo-treated women, total cholesterol levels were significantly lower only in women treated with CEE plus MPA regimens, probably reflecting the lesser increase in HDL-C Table 2and Figure 1, bottom right).

Blood Pressure

There were no significant differences in systolic blood pressure among treatment groups Table 2. Mean systolic blood pressure levels decreased slightly during the first year and increased thereafter in all groups, including women assigned to placebo Figure 2, left). Diastolic blood pressure also did not vary significantly by treatment assignment Table 2and Figure 2, right). Results were similar in analyses stratified by hysterectomy status.

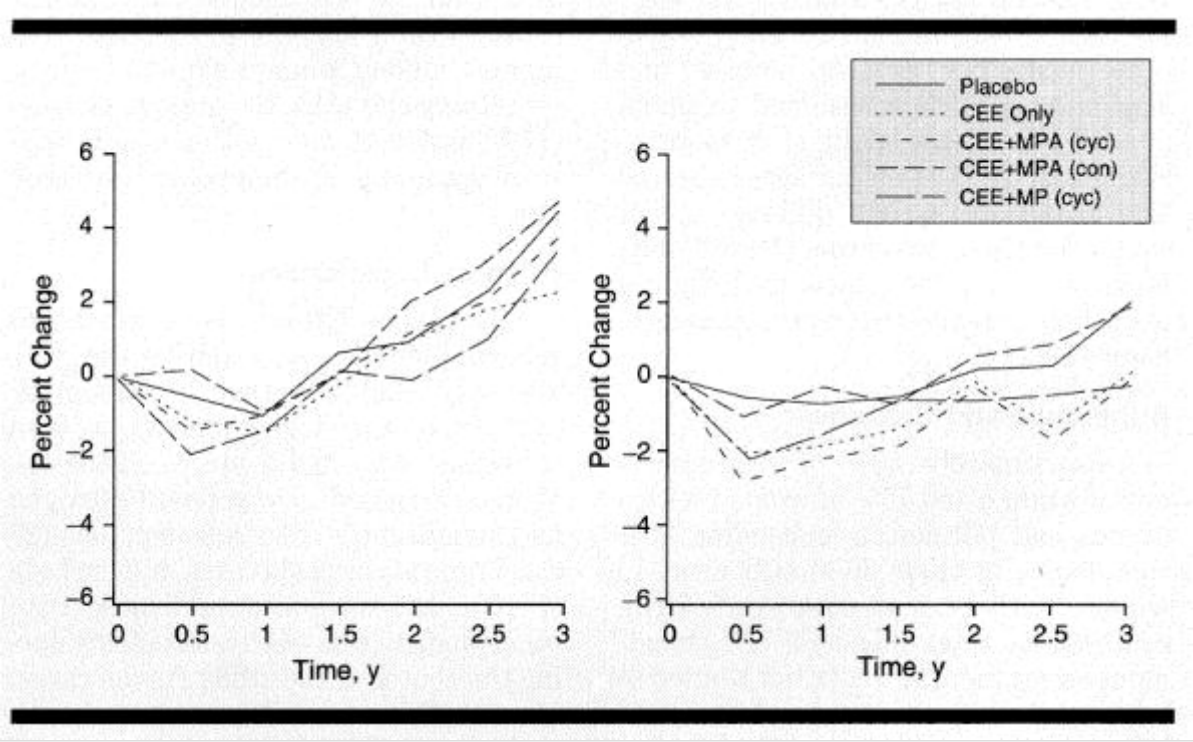

Figure 2. Mean percent change from baseline by treatment arm for systolic (left) and diastolic (right) blood pressure. See Table 1for explanation of treatment groups

Glucose and Insulin

Mean changes in 2-hour insulin, the primary outcome measure for carbohydrate metabolism, did not differ significantly by treatment assignment Table 2. An unexplained downward drift in postchallenge insulin levels occurred between the first follow-up year and the end of the trial Figure 3, left). This trend was similar in all treatment groups and in women with and without a hysterectomy.

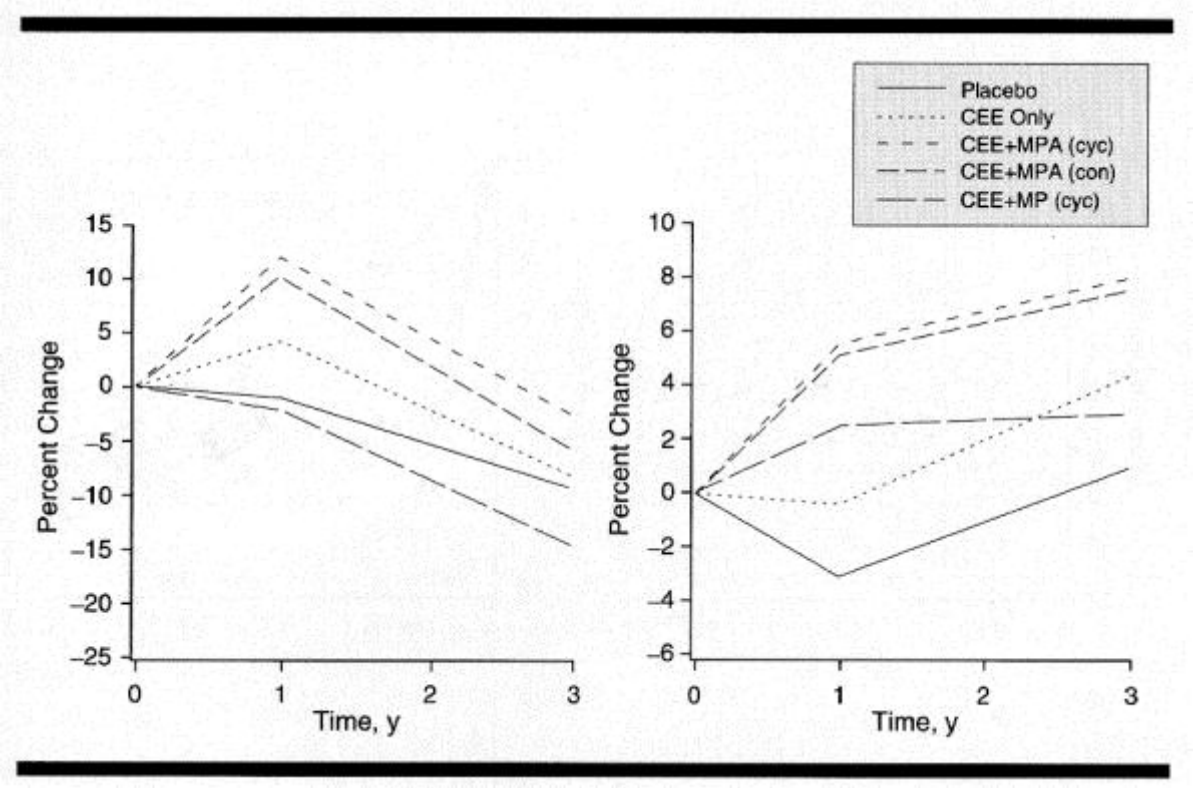

Figure 3. Mean percent change form baseline by treatment arm for 2-hour insulin (left) and 2-hour glucose (right). See Table 1for explanation of treatment groups

The decrease in insulin was not paralleled by a decrease in postchallenge glucose levels. Two-hour glucose levels increased significantly in women assigned to active treatment compared with placebo (P=.01). The largest differences from placebo were seen in women treated with CEE plus cyclic MPA (P=.05) or CEE plus continuous MPA (P=.02).

Fasting insulin levels decreased slightly but not significantly in women assigned to active treatments. Fasting glucose levels decreased slightly and significantly in all active treatment arms compared with placebo (P=.03). The difference between women assigned to placebo versus unopposed CEE was also significant (P<.04).

Fibrinogen

Changes in fibrinogen levels varied significantly by treatment assignment (Bonferroni P<.001) Table 2and Figure 4. In pairwise comparisons, women assigned to placebo had greater increases in fibrinogen than women assigned to active treatment (0.10 g/L vs -0.02 to 0.06 g/L, respectively) (all Bonferroni P<=.02). There were no significant differences between active treatment groups. Patterns were similar among women with and without a uterus.

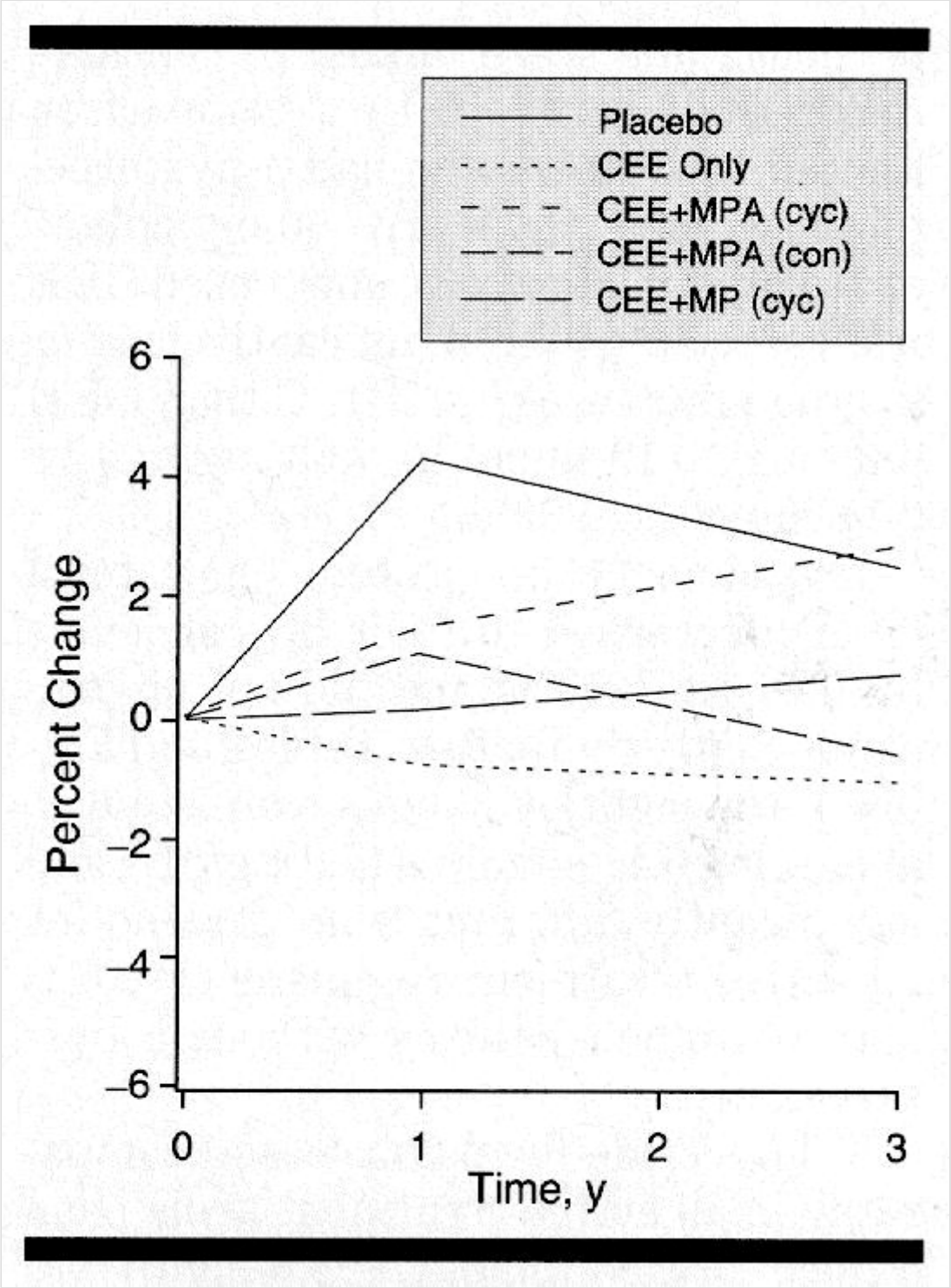

Figure 4. Mean percent change from baseline treatment arm for fibrinogen. See Table 1for explanation of treatment groups

Weight and Waist-Hip Ratio

Women in all treatment groups gained weight. Mean changes from baseline were greatest among women assigned to placebo (mean, 2.1 kg at 36 months) and least among women assigned to unopposed CEE (mean, 0.7 kg at 36 months) Table 2. Pairwise comparisons indicated that changes in weight differed significantly for these two arms (P=.03) only. Mean waist-hip ratio increased slightly over time, unrelated to treatment assignment Table 2.

Adherence and Crossover

Approximately 80% of hysterectomized women and 75% of women with a uterus had pill counts exceeding 80% compliance at their 36-month visit. In women without a uterus, study drug continuation rates did not differ by treatment assignment (P=.13), but tended to be lowest overall in placebo-treated women (67% vs 80% to 89% in other groups). In women with a uterus, however, continuation rates were lowest (63%) in women assigned to CEE, compared with 79% to 84% in other groups (P<.001). This difference was largely explained by the higher rates of adenomatous or atypical endometrial hyperplasia in women assigned to unopposed estrogen, who were required by PEPI protocol to discontinue the assigned therapy. The cumulative percent of women with a uterus who were unable to continue unopposed estrogen therapy for any reason was 20% at year 1, 45% at year 2, and 55% at year 3.

Ninety-seven percent of the 875 randomized women participated in the final 36-month evaluation. At the end of the trial, 6% of women with a hysterectomy and 8% of women without a hysterectomy were taking another hormone regimen than the one assigned at randomization Table 3. The percentage was highest among women who had a hysterectomy and were assigned to placebo (17%) and in women with a uterus who were assigned to unopposed estrogen (18%).

Table 3.—Adherence and Crossover Status of 847 PEPI Women Who Attended Close-Out Examinations by Uterus Status*

	Treatment Group				
	Placebo (n=165)	CEE Only (n=170)	CEE+MPA (cyc) (n=169)	CEE+MPA (con) (n=170)	CEE+MP (cyc) (n=173)
Taking initially assigned study drug, %					
Hysterectomy	75	81	91	87	82
No hysterectomy	83	46	81	86	82
Taking another HRT, %					
Hysterectomy	17	3	0	6	7
No hysterectomy	9	18	6	3	3
Not taking initially assigned study drug or other HRT, %					
Hysterectomy	8	16	9	8	11
No hysterectomy	8	36	13	11	15
Attendance, %	95	97	97	98	97

*See Table 1 for explanation of treatment groups. HRT indicates hormone replacement therapy.

Table 3. Adherence and Crossover Status of 847 PEPI Women Who Attended Close-Out Examinations by Uterus Status

Adverse Experiences

There were 110 adverse experiences reported for 97 women during the trial. The only conditions that varied significantly by treatment assignment were seen in women who had a uterus Table 4. Women assigned to unopposed estrogen had significantly more adenomatous (27 cases) and atypical (14 cases) hyperplasia (P<.001) and were also more likely than other women to have a hysterectomy during the course of the study (seven cases) (P=.04). Two women, one treated with unopposed estrogen and one treated with placebo, had localized endometrial cancer that progressed from atypia; they were successfully treated with hysterectomy. Hysterectomies were also performed for atypia (n=6), adenomatous hyperplasia (n=1), fibroid tumors (n=2), pelvic mass (n=2), and abnormal vaginal bleeding (n=1).

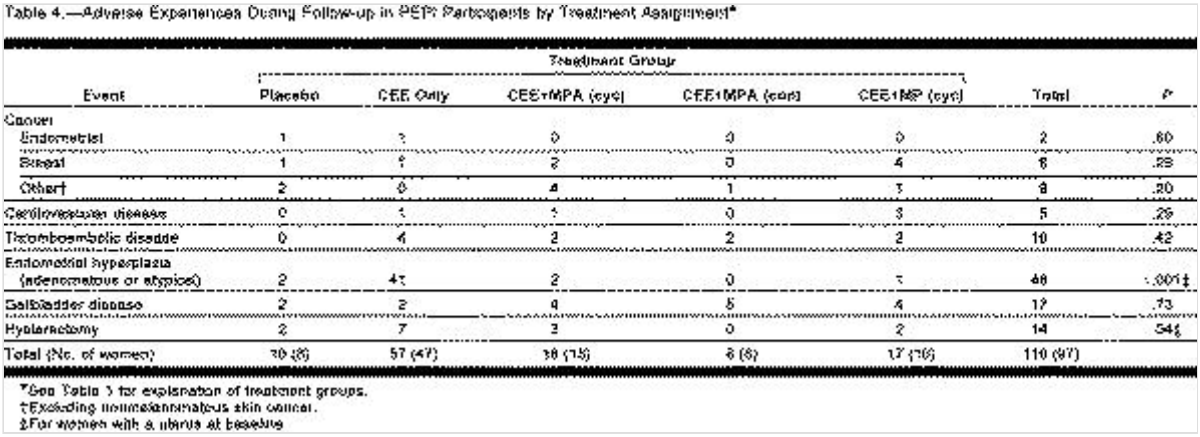

Table 4.—Adverse Experiences During Follow-up in PEPI Participants by Treatment Assignment*

Event	Treatment Group						
	Placebo	CEE Only	CEE+MPA (cyc)	CEE+MPA (cont)	CEE+MP (cyc)	Total	P
Cancer							
Endometrial	1	2	0	0	0	2	.60
Breast	1	2	2	0	4	8	.23
Other†	2	0	4	1	1	8	.20
Cardiovascular disease	0	1	1	0	3	5	.29
Thromboembolic disease	0	4	2	2	2	10	.42
Endometrial hyperplasia (adenomatous or atypical)	2	42	2	0	2	48	<.001‡
Gallbladder disease	2	2	4	5	4	17	.73
Hysterectomy	2	7	3	0	2	14	.54‡
Total (No. of women)	30 (8)	57 (47)	38 (15)	8 (6)	17 (10)	110 (97)	

*See Table 1 for explanation of treatment groups.
†Excluding nonmelanomatous skin cancer.
‡For women with a uterus at baseline

Table 4. Adverse Experiences During Follow-up in PEPI Participants by Treatment Assignment

Eight women developed breast cancer during the 3-year follow-up, including two diagnosed between 6 months and 1 year of randomization (one assigned to CEE and cyclic MP; one to CEE and cyclic MPA). Three other breast cancers were diagnosed at the first annual examination (two CEE and cyclic MP; one CEE and cyclic MPA). Other cancers included one apocrine, two colon, one primary liver, one unknown primary metastatic to liver, two lung, and one melanoma. Cardiovascular events included one cardiac arrest, one cerebral vascular accident, one transient ischemic attack, and two myocardial infarctions. Thromboembolic events included two women with pulmonary embolus, two with deep vein thrombosis, and six with superficial phlebitis. There were three deaths during the PEPI Trial, one each of breast cancer (CEE and MP), liver cancer (CEE and MP), and lung cancer (CEE and cyclic MPA).

Permanent interruption of study medication was required by protocol for possibly estrogen-dependent tumors and for stroke, transient ischemic attack, pulmonary embolus, deep vein thrombosis, and adenomatous or atypical endometrial hyperplasia Table 4. (Two participants with endometrial hyperplasia were allowed to resume study medication after hysterectomy.) Permanent interruption of study drug also occurred in women with cardiac arrest, myocardial infarction, and most other cancers.

Unblinding

A monitoring gynecologist (separate from the PEPI clinic staff) reviewed reports of unscheduled or unusual bleeding and could request information about treatment assignment from the coordinating center in order to assess the need for special treatment. This partial unblinding was not revealed to PEPI clinic staff or participants unless necessary for treatment. Only 39 women (4%) were unblinded and informed of their treatment assignment; 32 of them were taking unopposed estrogen.

COMMENT

HDL-C and Related Lipids and Lipoproteins

The PEPI Trial provides the most unequivocal evidence to date that unopposed estrogen has a more favorable effect on HDL-C than estrogen given with continuous or cyclic synthetic progestin. Women treated with estrogen and MP had significantly higher HDL-C levels than women treated with estrogen and MPA. In women without a uterus, mean HDL-C levels increased more with CEE alone than with CEE plus MP. Nevertheless, all hormone treatments were significantly better than placebo, and HDL-C averaged 0.06 mmol/L (2.4 mg/dL) higher in women treated with the least effective of the active regimens, compared with placebo-treated women. All active treatments lowered LDL-C; the least effective of the active regimens lowered LDL by an average of 0.26 mmol/L (10.1 mg/dL) relative to placebo.

These results are concordant with most smaller and shorter clinical trials, which found that women taking oral unopposed estrogen had greater increases in HDL-C than women taking estrogen in combination with a synthetic progestin [11,12,14,24]. They are also in agreement with a small clinical trial [29] suggesting that MP preserves most of oral estrogen's favorable effect on HDL-C.

In women, HDL-C is more closely related to cardiovascular disease than LDL-C [41]. Despite strong inverse associations between HDL-C levels and heart disease risk [15,16,17], no clinical trials have been performed to show that increasing HDL-C reduces heart disease risk in women. In observational studies of men, an increase of 0.026 mmol/L (1 mg/dL) in HDL-C was associated with a 2% decrease in the risk of heart disease [42]. The effect appears to be greater in women: in observational studies, a 0.1- to 0.13-mmol/L (4- to 5-mg/dL) increment in HDL-C, as observed here with unopposed CEE or CEE with MP, was associated with a 20% to 25% decrease in the risk of coronary heart disease [15,16]. The consequences of the smaller increments observed when estrogen was given with either continuous or cyclic MPA (0.05-mmol/L vs 0.13-mmol/L (2- mg/dL vs 5-mg/dL) increase) are potentially large.

The present data also confirm other studies showing that estrogen decreases LDL-C when taken with or without a progestin [8,11,12,13]. Unfortunately, there are few observational data and no clinical trial data to show that LDL-C is as important a heart disease risk factor in women as in men. Nevertheless, the average 0.41-mmol/L (15.9-mg/dL) decrease in LDL-C observed here is large and might be expected to reduce cardiovascular risk.

Contrary to most previous studies [14], all groups of hormone-treated women had significantly increased triglyceride levels that did not differ between women assigned to estrogen alone or with a progestin. Estrogen increases triglyceride levels by increasing production, not by impaired clearance, and these changes may not be atherogenic [43,44]. Triglyceride levels remained less than 12.9 mmol/L (500 mg/dL) for all but 11 PEPI women, well below the level associated with pancreatitis [45]. However, women with baseline triglyceride levels greater than 12.9 mmol/L (500 mg/dL) were excluded, and these are the women who would be at greatest risk.

Blood Pressure

Because noncontraceptive estrogens increase plasma renin substrate [46,47], it is plausible that they would also increase blood pressure. Earlier studies variously reported increases, decreases, or no change in blood pressure in women treated with estrogen [48,49]. These trials typically gave a wide variety of treatment regimens for only a few months to relatively small numbers of women. Most did not use standardized methods for measuring blood pressure and obtained only a single measure of blood pressure at baseline. In the PEPI Trial, the baseline blood pressure was the average of four blood pressures measured at two separate visits by certified technicians who used standardized methods.

In PEPI women, hormone replacement did not adversely affect blood pressure. The early decrease in blood pressure probably represents "white coat hypertension" or regression to the mean; the average overall increase in systolic blood pressure paralleled a modest concurrent increase in body weight in all treatment groups. These results are concordant with a recent prospective study of estrogen in hypertensive menopausal women, who also gained weight but did not increase their blood pressure [50].

Insulin and Glucose

In PEPI women, postchallenge insulin levels did not differ significantly by treatment assignment. At the same time, 2-hour glucose levels increased in all active treatment groups; compared with placebo, this increment was statistically significant only in women assigned to either of the two CEE plus MPA regimens (P<=.05). The discordance between insulin and glucose levels has been reported previously [23,51].

These PEPI findings contrast with results reported from a large cross-sectional study [23] that found lower 2-hour insulin levels in postmenopausal women taking estrogen alone or with a progestin. As reviewed elsewhere [49,52], some small clinical trials suggested that oral estrogen improved glucose tolerance; few of these studies considered insulin levels. A recent 1-year trial [24] in 525 women who were treated with unopposed CEE or one of four other CEE plus MPA regimens reported a significant decrease in postchallenge insulin in all treatment groups similar to the changes observed in our study; that study had no placebo control group [24]. The unexplained decrease in 2-hour insulin levels during the PEPI trial would have led to erroneous conclusions had there been no placebo group.

The finding that hormones did not alter postchallenge insulin levels does not exclude the possibility that estrogen has a beneficial effect on carbohydrate metabolism. Fasting insulin may be a better marker for insulin resistance than postchallenge insulin [53]. Fasting insulin (and glucose) levels were slightly lower in women assigned to active treatment. Reduced fasting insulin [51] or reduced insulin resistance [54] has been reported in postmenopausal women treated with some oral estrogens, although less so when MPA is added [52,55].

Fibrinogen

In PEPI, fibrinogen levels increased in women assigned to placebo but remained fairly stable among women assigned to active treatment. The maximum pairwise difference (0.11 g/L) is similar to results obtained in some observational studies and several small clinical trials, in which fibrinogen levels were significantly lower in women taking estrogen alone or estrogen plus progestin than in untreated postmenopausal women [22,56]. A difference of this magnitude more than doubled the risk of heart disease in Framingham women [57].

Possible Explanations for Absent Associations

At the beginning of PEPI, more was known about the effect of unopposed estrogen on HDL-C than about any other primary endpoint chosen for study. Consequently, sample size and power calculations were heavily dependent on expected differences in HDL-C in estrogen-treated women. For systolic blood pressure, the study protocol power calculations for a mean effect size with 80% power were 5 mm Hg, whereas the maximum observed effect size was 1.7 mm Hg. Although we cannot exclude a small effect, data Figure 2, left) do not suggest any consistent pattern.

When PEPI was planned, the effect size of hormone treatment projected to be associated with 2-hour insulin levels was 189 pmol/L. Post hoc calculations indicate that PEPI provided 80% statistical power to detect mean differences of 82 pmol/L. The largest mean difference observed was 39 pmol/L. Therefore, differences cannot be excluded, although the observed pattern Figure 3, left) shows no evidence of divergence in insulin levels with any of the active regimens. The downward drift in insulin levels is unexplained, but the concordance with assays repeated later suggests that the relative ranking for participant values remained essentially the same despite the downward drift.

The Bonferroni adjustment is a conservative control for the problem of multiple comparisons, but its use is unlikely to have obscured associations here. Conclusions were similar (significant for HDL-C and fibrinogen, and nonsignificant for blood pressure and insulin) before and after the Bonferroni adjustment. None of the primary endpoints met conventional levels of statistical significance ($P<.05$) before but not after adjusting for multiple comparisons.

Compliance in PEPI was assessed only by self-report and pill count. It seems unlikely that misclassification of adherence explains the absent associations, because the observed changes in HDL-C and fibrinogen were of the expected magnitude.

Generalizability

Despite targeted recruitment efforts, there were too few minority women to test for ethnic differences in hormonal effects. There are no known differences in estrogen metabolism by ethnic status that suggest nonwhite women would be less (or more) responsive. Although the PEPI cohort was a more highly educated group than US women in general, participation after the first screening visit was unrelated to level of education. Although women with serious illnesses were excluded, healthy volunteer bias was minimized because 60% of women who attended the preliminary screening visit were randomized. The PEPI women resemble similarly aged women in the United States with regard to their gynecologic histories and the distribution of their values for primary PEPI endpoints and covariates. The largest difference between PEPI women and women in general is likely to be the 80% compliance observed in PEPI women compared with 15% to 50% compliance in clinic populations [58].

Unmeasured Heart Disease Risk Factors

For fiscal and design reasons, not all of the potentially interesting heart disease risk factors could be studied in PEPI. Estrogen has been credited with a long list of plausible protective mechanisms, some of which have been demonstrated under experimental conditions after the primary endpoints for PEPI had been chosen. For example, estrogen has been proposed or shown to be a calcium channel blocker, an antioxidant, a vasodilator, and a homocysteinemia reducer [7,8,9]. Recent studies offer considerable support for cardioprotection due in part to estrogen-augmented blood flow [10,59,60], an observation compatible with greater benefit associated with current (as opposed to past) hormone use in observational studies [61]. If one or more of these attributes is a major mechanism for estrogen's protective effects, then the decision to use estrogen, or the choice of regimen, could be relatively independent of its effects on lipids, lipoproteins, and clotting factors. In the absence of proof of this hypothesis, it seems logical to recommend the hormone therapy that has the most favorable effect on HDL-C, particularly when heart disease prevention figures prominently in the rationale for treatment.

Recommendations

Heart disease is the most common cause of death in women in nearly all industrialized countries. If estrogen-mediated cardiovascular protection is of the magnitude seen in many observational studies, a 50% reduction in cardiac deaths would be expected to overwhelm the possible risk of endometrial or breast cancer and the possible benefit of fewer osteoporotic fractures in postmenopausal women [3].

In a treatment prevention program, most individuals receive no benefit [62]. Therefore, cancer risks, however small, cannot be ignored. Active treatment was not associated with an excess risk of breast cancer in PEPI women, all of whom were required to have a negative mammogram at baseline. However, a 3-year trial is too short and the numbers of women in the PEPI trial too small to exclude an excess risk with longer use.

In the overall context of risk and benefit, PEPI trial data uniquely document the utility of regular endometrial biopsy for the detection of reversible hyperplasia and the unacceptability of unopposed estrogen for women with a uterus who are not under annual endometrial surveillance. Adenomatous or atypical endometrial hyperplasia, potentially precancerous lesions, developed in one third of women with an intact uterus who were assigned to unopposed estrogen. This rate was higher than predicted, but no previous study of this duration with annual endometrial biopsies has been reported. When detected early, estrogen-induced hyperplasia is reversible, and the two early cancers (one cancer in situ, and one stage I in a placebo-treated woman) observed in PEPI women were treated successfully by hysterectomy.

The prevention of osteoporotic fracture is the major accepted indication for long-term estrogen therapy today [3]. It is not known whether different hormone regimens differ significantly with regard to the prevention of osteoporotic fracture. However, even if one hormone regimen should prove much more effective than others against osteoporosis, it will be important to consider also the expected effect of that treatment on heart disease prevention because heart disease is more common than osteoporotic fractures in older women [3].

Large clinical trials are currently under way in the United States to determine whether (and how much) hormone therapy will reduce the risk of heart disease in healthy women (Women's Health Initiative) or the risk of new cardiovascular events in women who already have heart disease (Hormone Estrogen/Progestin Replacement Study), but neither of these studies is expected to provide results for at least 5 years. Until data are available, it seems logical that the optimal treatment for the prevention of heart disease is the safest regimen with the most favorable effects on heart disease risk factors.

CONCLUSIONS

The PEPI study confirms that oral estrogen taken alone or with MPA or MP is associated with improved lipoprotein and lower fibrinogen levels compared with placebo and shows that the magnitude of these differences is likely to be clinically significant. PEPI also demonstrates that there are significant losses with regard to HDL-C, the most important readily measured determinant of cardioprotection in women, when MPA is added to estrogen therapy. However, the 10% per year rate of adenomatous or atypical endometrial hyperplasia observed in women assigned to unopposed estrogen makes combination hormone therapy prudent, if not mandatory, for women with a uterus. For these women, estrogen plus MP appears to spare the endometrium and to preserve the bulk of estrogen's favorable effects on risk factors including HDL-C.

THE PEPI TRIAL GROUP

Clinical Centers: George Washington University, Washington, DC: Valery T. Miller, MD (principal investigator and writing group) (previously, John LaRosa, MD, writing group); Vanessa Barnabei, MD, PhD, Craig Kessler, MD (coinvestigators); Ginny Levin, Ann Smith-Roth, Margaret Griffin, RN, PA, Diane B. Stoy, RN, BS, PhD. The Johns Hopkins University, Baltimore, Md: Trudy Bush, PhD (principal investigator and writing group); Howard Zacur, MD, PhD; David Foster, MD (coinvestigators); Jean Anderson, MD, Alice McKenzie, MS, Susan Miller, ScD. Stanford (Calif) University: Peter D. Wood, DSc (principal investigator and writing group); Marcia L. Stefanick, PhD (writing group), Robert Marcus, MD (coinvestigators); Allison Akana, PA, W. LeRoy Heinrichs, MD, Charlene Kirchner, RD, Katherine O'Hanlan, MD, Melissa Ruyle, Mary Sheehan, MS. The University of California, Los Angeles: Howard L. Judd, MD (principal investigator and writing group); Gail Greendale, MD (coinvestigator and writing group); Richard Bayalos, MD, Kathy Lozano, RNP, Kathy Kawakami, RN. The University of California, San Diego: Elizabeth Barrett-Connor, MD (principal investigator and writing group); Robert Langer, MD (coinvestigator and writing group); Donna Kritz-Silverstein, PhD, Mary Lou Carrion-Petersen, RN, Carmela Cavero, MS, CNM. The University of Iowa, Ames: Helmut G. Schrott, MD (principal investigator and writing group); Susan R. Johnson, MD (coinvestigator); Deborah A. Feddersen, RN, Denise L. Krutzfeldt, Jo Ann Benda, MD. The University of Texas Health Science Center, San Antonio: Carl Pauerstein, MD (principal investigator); Jose Trabal, MD (coinvestigator and writing group); Robert Schenken, MD, Michael P. Stern, MD, Mercedes Rodriguez-Sifuentes, RN, Carann Easton, RN. Coordinating Center: The Bowman Gray School of Medicine: H. Bradley Wells, PhD (principal investigator and writing group); Mark Espeland, PhD (writing group), George Howard, DrPh, Robert Byington, PhD, Claudine Legault, PhD, Sally Shumaker, PhD (coinvestigators); Patricia Hogan, MS (writing group), Don Hire, BS, Carol Wasilauskas, MS, Margaret James, MS, Kathy Lane, BS, Tim Terrell, MS, Stephanie Reece, BS, June Pierce, AB (writing group), Mary Snow, Susan Anthony, BS. Participating Institutes of the National Institutes of Health: National Heart, Lung, and Blood Institute: Irma L. Mebane-Sims, PhD (program administrator and writing group); Paula Einhorn, MD, Sally Hunsberger, PhD, Myron Waclawiw, PhD (previously, Ken Lippel, PhD, Diane Lucas, PhD, Joel Verter, PhD, Sherry Jackson, MD). National Institute of Child Health and Human Development: Joseph Kelaghan, MD (liaison) (previously, Jeffrey Perlman, MD, Pam Wolf, PhD). National Institute of Arthritis and Musculoskeletal and Skin Diseases: Joan McGowan, PhD (liaison) (previously, Stephen Gordon, PhD, Stephen Heyse, MD). National Institute of Diabetes and Digestive and Kidney Diseases: Judith Fradkin, MD (liaison). National Institute on Aging: Sherry Sherman, PhD (liaison) (previously, Lot Page, MD, Ann Sorenson, PhD). Data and Safety Monitoring Board: Barbara Hulka, MD (chair); Baruch Brody, PhD, Ronald Burkman, MD, Robert Heaney, MD, Ronald Krauss, MD, Harold Roberts, MD, Janet Wittes, PhD (members)(previously, Lawrence Riggs, MD). Central Facilities: Drug Distribution Center, Public Health Services, Health Resources and Services Administration, Supply Service Center, Perry Point, Md: Cpt Richard Moss. Lipid Laboratory, Seattle, Wash: Northwest Lipid Research Center, John Albers, PhD, Santica Marcovina, PhD. Glucose/Insulin Laboratory, Indianapolis, Ind: Wishard Memorial Hospital, S. Edwin Fineberg, PhD. Hemostasis Laboratory, Burlington, Vt: University of Vermont, Russell P. Tracy, PhD. Pathology Laboratory, Bethesda, Md: National Cancer Institute, Maria Merino, MD. Pathology Arbiter, Boston, Mass: Massachusetts General Hospital, Robert Scully, MD (previously, Virginia Livolsi, MD). Laboratory Consultant: The Jewish Hospital of St Louis, Gerald Kessler, PhD.

The Postmenopausal Estrogen/Progestin Interventions Trial was supported by cooperative agreement research grants (U01-HL40154, U01-HL40185, U01-HL40195, U01-HL40205, U01-HL40207, U01-HL40231, U01-HL40232, and U01-HL40273) from the National Heart, Lung, and Blood Institute; the National Institute of Child Health and Human Development; the National Institute of Arthritis and Musculoskeletal and Skin Diseases; the National Institute of Diabetes and Digestive and Kidney Diseases; and the National Institute on Aging.

REFERENCES

1. Bush TL. Noncontraceptive estrogen use and risk of cardiovascular disease: an overview and critique of the literature. In: Korenman SG, ed. The Menopause: Biological and Clinical Consequences of Ovarian Failure; Evolution and Management. Norwell, Mass: Serono Symposia; 1990:211-224. [Context Link]

2. Stampfer MJ, Colditz GA. Estrogen replacement and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med. 1991;20:47-63. Bibliographic Links | [Context Link]

3. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med. 1992;117:1016-1037. Bibliographic Links | [Context Link]

4. Hunt K, Vessey M, McPherson K, Coleman M. Long-term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. Br J Obstet Gynaecol. 1987;94:620-635. Bibliographic Links | [Context Link]

5. Falkeborn M, Persson I, Adami HO, et al. The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement. Br J Obstet Gynaecol. 1992;99:821-828. Bibliographic Links | [Context Link]

6. Psaty BM, Heckbert SR, Atkins D, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. Arch Intern Med. 1994;154:1333-1339. Bibliographic Links | [Context Link]

7. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. JAMA. 1991;265:1861-1867. Bibliographic Links | [Context Link]

8. Tikkanen MJ. Mechanisms of cardiovascular protection by post menopausal hormone replacement therapy. Cardiovasc Risk Factors. 1993;3:138-143. [Context Link]

9. Riedel M, Rafflenbeul W, Lichtlen P. Ovarian sex steroids and atherosclerosis. Clin Invest. 1993;71:406-412. Bibliographic Links | [Context Link]

10. Gangar KF, Reid BA, Crook D, Hillard TC, Whitehead MI. Oestrogens and atherosclerotic vascular disease: local vascular factors. Baillieres Clin Endocrinol Metab. 1993;7:47-59. Bibliographic Links | [Context Link]

11. Miller VT. Dyslipoproteinemia in women: special considerations. Endocrinol Metab Clin North Am. 1990;19:381-398. Bibliographic Links | [Context Link]

12. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. N Engl J Med. 1991;325:1196-1204. Buy Now | Bibliographic Links | [Context Link]

13. Lobo RA. Effects of hormonal replacement on lipids and lipoproteins in postmenopausal women. J Clin Endocrinol Metab. 1991;73:925-930. Bibliographic Links | [Context Link]

14. Rijpkema AH, van der Sanden AA, Ruijis AH. Effects of post-menopausal oestrogen-progestogen replacement therapy on serum lipids and lipoproteins: a review. Maturitas. 1990;12:259-285. [Context Link]

15. Goldbourt U, Medalie JH. High density lipoprotein cholesterol and incidence of coronary heart disease: the Israeli Ischemic Heart Disease Study. Am J Epidemiol. 1979;109:296-308. Bibliographic Links | [Context Link]

16. Castelli WP. Cardiovascular disease in women. Am J Obstet Gynecol. 1988;158:1553-1560. Bibliographic Links | [Context Link]

17. Bass KM, Newschaffer CJ, Klag MJ, Bush TL. Plasma lipoprotein levels as predictors of cardiovascular death in women. Arch Intern Med. 1993;153:2209-2216. [Context Link]

18. Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-Up Study. Circulation. 1987;75:1102-1109. Ovid Full Text | Bibliographic Links | [Context Link]

19. Gruchow HW, Anderson AJ, Barboriak JJ, Sobocinski VA. Postmenopausal use of estrogen and occlusion of coronary arteries. Am Heart J. 1988;115:954-963. Bibliographic Links | [Context Link]

20. Tikkanen MJ, Kuusi T, Nikkila EA, Sipinen S. Post-menopausal hormone replacement therapy: effects of progestogens on serum lipids and lipoproteins: a review. Maturitas. 1986;8:7-17. [Context Link]

21. Newnham HH. Oestrogens and atherosclerotic vascular disease: lipid factors. Baillieres Clin Endocrinol Metab. 1993;7:61-93. Bibliographic Links | [Context Link]

22. Nabulsi AA, Folsom AR, White A, et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. N Engl J Med. 1993;328:1069-1075. Buy Now | Bibliographic Links | [Context Link]

23. Barrett-Connor E, Laakso M. Ischemic heart disease risk in postmenopausal women: effects of estrogen use on glucose and insulin levels. Arteriosclerosis. 1990;10:531-534. [Context Link]

24. Lobo RA, Pickar JH, Wild RA, Walsh B, Hirvonen E. Metabolic impact of adding medroxyprogesterone acetate to conjugated estrogen therapy in postmenopausal women. Obstet Gynecol. 1994;84:987-995. [Context Link]

25. The PEPI Investigators. The Postmenopausal Estrogen/Progestins Interventions Trial: rationale, design, and conduct. Control Clin Trials. In press. [Context Link]

26. The PEPI Investigators. Baseline characteristics of women in the Postmenopausal Estrogen/Progestins Interventions Trial. Control Clin Trials. In press. [Context Link]

27. The PEPI Investigators. The recruitment of healthy postmenopausal women for a multicenter trial: the Postmenopausal Estrogen/Progestins Interventions (PEPI) experience. Control Clin Trials. In press. [Context Link]

28. The PEPI Investigators. The Postmenopausal Estrogen/Progestins Interventions Trial: physical and laboratory measurements. Control Clin Trials. In press. [Context Link]

29. Moorjani S, Dupont A, Labrie F, et al. Changes in plasma lipoprotein and apolipoprotein composition in relation to oral versus percutaneous administration of estrogen alone or in cyclic association with utrogestan in menopausal women. J Clin Endocrinol Metab. 1991;73:373-379. Bibliographic Links | [Context Link]

30. Jensen J, Riis BJ, Strom V, Nilas L, Christiansen C. Long-term effects of percutaneous estrogens and oral progesterone on serum lipoproteins in postmenopausal women. Am J Obstet Gynecol. 1987;156:66-71. Bibliographic Links | [Context Link]

31. Hypertension Detection and Follow-up Program Cooperative Group. Variability of blood pressure and the results of screening in the Hypertension Detection and Follow-up Program. J Chronic Dis. 1978;31:651-667. Bibliographic Links | [Context Link]

32. Warnick GR. Enzymatic methods for quantification of lipoprotein lipids. Methods Enzymol. 1986;129:101-123. Bibliographic Links | [Context Link]

33. Bachorik PS, Albers JJ. Precipitation methods for quantification of lipoproteins. Methods Enzymol.1986;129:78-100. Bibliographic Links | [Context Link]

34. Hainline A, Karon J, Lippel K, eds. Manual of Laboratory Operations:Lipid Research Clinics Program, Lipid and Lipoprotein Analysis. 2nd ed. Washington, DC: National Institutes of Health, US Dept of Health and Human Services; 1982. [Context Link]

35. Trinder P. Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann Clin Biochem. 1969;6:24. [Context Link]

36. Morgan CR, Laarow A. Immunoassay of insulin--two antibody system: plasma levels of normal, subdiabetic and diabetic rats. Diabetes. 1963;12:115-126. [Context Link]

37. Clauss A. Gerinnungs physiologische Schnellmethode zur Bestimmung des Fibrinogens. Acta Haematol. 1957;17:237-246. [Context Link]

38. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics. 1982;38:963-974. Bibliographic Links | [Context Link]

39. SAS Institute Inc. Changes and enhancements. In: SAS Technical Report P-229, SAS/SAT Software, Release 6.07. Cary, NC: SAS Institute Inc; 1992. [Context Link]

40. Edwards AL. Experimental Design in Psychological Research. 5th ed. New York, NY: Harper & Row Publishers Inc; 1985. [Context Link]

41. Jacobs DR, Mebane IL, Bangdiwala SI, Criqui MH, Tyroler HA. High density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men and women: the follow-up study of the Lipid Research Clinics Prevalence Study. Am J Epidemiol. 1990;131:32-47. Bibliographic Links | [Context Link]

42. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. Circulation. 1989;79:8-15. Ovid Full Text | Bibliographic Links | [Context Link]

43. Walsh BW, Sacks FM. Effects of low dose oral contraceptives on very low density and low density lipoprotein metabolism. J Clin Invest. 1993;91:2126-2132. Bibliographic Links | [Context Link]

44. Sacks FM, Walsh BW. Sex hormones and lipoprotein metabolism. Curr Opin Lipidol. 1994;5:236-240. [Context Link]

45. Glueck CJ, Lang J, Hamer T, Tracy T. Severe hypertriglyceridemia and pancreatitis when estrogen replacement therapy is given to hypertriglycleridemic women. J Lab Clin Med. 1994;123:59-64. [Context Link]

46. Mashchak CA, Lobo RA, Donozo-Takano R, et al. Comparison of pharmacodynamic properties of various estrogen formulations. Am J Obstet Gynecol. 1982;144:511-518. Bibliographic Links | [Context Link]

47. Hassager C, Riis BJ, Strom V, Guyene TT, Christiansen C. The long-term effect of oral and percutaneous estradiol on plasma renin substrate and blood pressure. Circulation. 1987;76:753-758. [Context Link]

48. Mashchak CA, Lobo RA. Estrogen replacement therapy and hypertension. J Reprod Med. 1985;30:805-810. Bibliographic Links | [Context Link]

49. Barrett-Connor E. Putative complications of estrogen replacement therapy: hypertension, diabetes, thrombophlebitis, and gallstones. In: Korenman SG, ed. The Menopause: Biological and Clinical Consequences of Ovarian Failure; Evolution and Management. Norwell, Mass: Serono Symposia; 1990:199-209. [Context Link]

50. Lip GYH, Beevers M, Churchill D, Beevers DG. Hormone replacement therapy and blood pressure in hypertensive women. J Hum Hypertens. 1994;8:491-494. Bibliographic Links | [Context Link]

51. Cagnacci A, Soldani R, Carriero PL, Paoletti AM, Fioretti P, Melis GB. Effects of low doses of transdermal 17beta-estradiol on carbohydrate metabolism in postmenopausal women. J Clin Endocrinol Metab. 1992;74:1396-1400. Bibliographic Links | [Context Link]

52. Stevenson JC, Proudler AJ, Walton C, Godsland IF. HRT mechanisms of action: carbohydrates. Int J Fertil Menopausal Stud. 1994;39:50-55. [Context Link]

53. Laakso M. How good a marker is insulin level for insulin resistance? Am J Epidemiol. 1993;137:959-965. Bibliographic Links | [Context Link]

54. Godsland IF, Gangar KF, Walton C, et al. Insulin resistance, secretion, and elimination in postmenopausal women receiving oral or transdermal hormone replacement therapy. Metabolism. 1993;42:846-853. Bibliographic Links | [Context Link]

55. De Cleyn K, Buytaert P, Coppens M. Carbohydrate metabolism during hormonal substitution therapy. Maturitas. 1989;11:235-242. Bibliographic Links | [Context Link]

56. Meilahn EN, Kuller LH, Matthews KA, Kiss JE. Hemostatic factors according to menopausal status and use of hormone replacement therapy. Ann Epidemiol. 1992;2:445-455. [Context Link]

57. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and the risk of cardiovascular disease: the Framingham Study. JAMA. 1987;258:1183-1186. Bibliographic Links | [Context Link]

58. Ravnikar VA. Compliance with hormone therapy. Am J Obstet Gynecol. 1987;156:1332-1334. Bibliographic Links | [Context Link]

59. Rosano GM, Sarrell PM, Poole-Wilson PA, Collins P. Beneficial effect of oestrogen on exercise-induced myocardial ischaemia in women with coronary artery disease. Lancet. 1993;342:133-136. Bibliographic Links | [Context Link]

60. Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO. Acute vascular effects of estrogen in postmenopausal women. Circulation. 1994;90:786-791. Ovid Full Text | Bibliographic Links | [Context Link]

61. Henderson BE, Paganini-Hill A, Ross RK. Estrogen replacement therapy and protection from acute myocardial infarction. Am J Obstet Gynecol. 1988;159:312-317. Bibliographic Links | [Context Link]

62. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985;14:32-38. Bibliographic Links | [Context Link]

IMAGE GALLERY

Select All

Export Selected to PowerPoint

Table 1

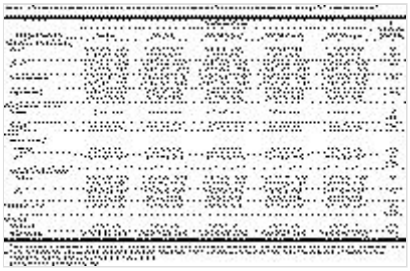

Table 2

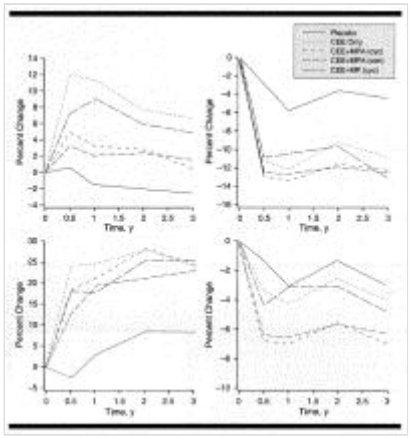

Figure 1

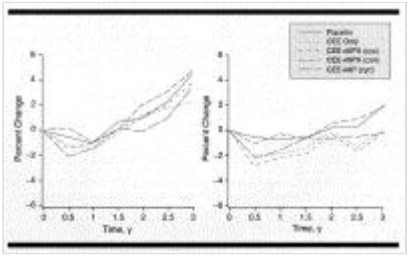

Figure 2

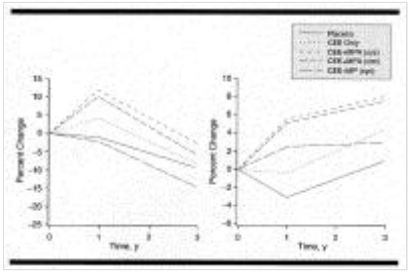

Figure 3

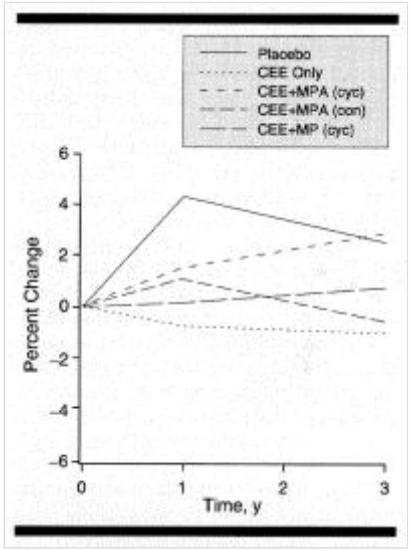

Figure 4

Table 4

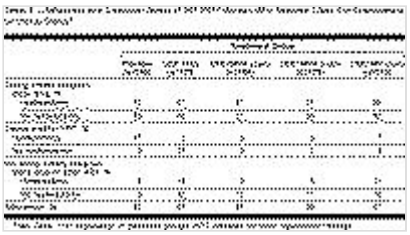

Table 3

Back to Top